IX-C. Blood Lipids

There are three lipids which are relevant in the consideration of the pathogenesis of atherosclerosis: Cholesterol, triglycerides and free fatty acids (Kershbaum and Bellet, 1966; Kershbaum, 1967; Mulcahy and Hickey, 1967; Boyle et al., 1968). The acute effects of smoking on the blood levels of these lipids are complex and varied. The smoking of 1 to 5 cigarettes has been reported by Göksel (1967) and Ciampolini et al. (1968) to increase the cholesterol level and by Butkus and Page (1965) and Page et al. (1959) not to influence it. For triglycerides, both an increase (Göksel, 1967) and no effect (Butkus and Page, 1965) have been reported.

The late Samuel Bellet and Alfred Kershbaum had investigated the effect of cigarette smoking on serum free fatty acids (FFA) in normal subjects. There was an elevation of FFA occurring 10 minutes after smoking cigarettes, and essentially no effect on serum cholesterol and triglycerides (Kershbaum et al., 1960, 1961). The increase of FFA in patients with healed myocardial infarct was greater than in normal subjects (Kershbaum et al., 1962). This increase is mediated through the adrenal glands and the sympathetic nervous system, because it was accompanied by an increase in urinary catecholamine excretion and the FFA response was blocked by sympathetic blocking drugs (Kershbaum et al., 1963; Kershbaum and Bellet, 1964). The thesis that they had developed was further elaborated by the following investigations: suppression of the free fatty acid response by ingestion of whiskey (Kershbaum et al., 1964), investigation of various

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forms of tobacco consumption in humans and dogs (Kershbaum et al., 1965, 1966; Kershbaum and Bellet, 1968; Kershbaum, 1968), and an increase in adrenocortical secretion accompanying the elevated FFA (Kershbaum et al., 1967a, 1967b; Kershbaum et al., 1968). Before Bellet died in 1971, he had completed the following sequence of conclusions as to how cigarette smoking causes elevation of the cholesterol level: (a) nicotine from tobacco releases catecholamines which mobilize FFA and lipoproteins; (b) in addition, catecholamines stimulate the anterior lobe of the pituitary gland to secrete adrenocorticotropic hormone (c) stimulation of the adrenal cortex releases hormones which play an essential and supportive role in the action of catecholamines on lipid metabolism.

The most important link in the above hypothesis is an increase in FFA following smoking. Several investigators have failed to observe an increase (Konttinen and Rajasalmi, 1963; Kedra et al., 1965; Frankl et al., 1966; Miturzyńska-Stryjecka et al., 1970). Furthermore smoking does not cause an elevation in blood sugar and epinephrinelike substances in the systemic blood (Rehder and Roth, 1959).

It has been difficult to obtain definitive proof that cigarette smoking causes an acute rise in blood lipids. Yet among habitual smokers there is an elevation in lipid levels as compared with nonsmokers (Harlan et al., 1967; Modzelewski and Malec, 1969; Tägert, 1970).

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IX-D. Blood Coagulation

Several investigations have been made in human subjects as to the fact that cigarette smoking causes an increase in coagulability of the blood (Murphy and Mustard, 1966). After smoking 1 to 10 cigarettes healthy young adults experience a shortening of clotting time and of thrombus formation time, and a decrease in fibrinolytic activity (Blackburn et al., 1959; Lisiewicz, 1963; Ambrus and Mink, 1964; Sogani and Joshi, 1965; Kedra and Korolko, 1965; Engelberg, 1965; Engelberg and Futterman, 1967; Engelberg and Engelberg, 1968; Schoendorf et al., 1970). It has been postulated by Engelberg (1965) that the hypercoagulability of blood is mediated by the release of epinephrine induced by nicotine. However, a proportionate dose response in the blood clotting system to the differing nicotine concentration could not be demonstrated by Schoendorf et al. (1970).

The acute effects of smoking on platelets include the following: no effect on total counts (Eisen and Hammond, 1956); shorter platelet survival time (Mustard and Murphy, 1963); increased platelet adhesiveness (Ashby et al., 1965; Engelberg and Futterman, 1966; Glynn et al., 1966; Murchison and Fyfe, 1966; El-Ebrashy et al., 1967; Facchini et al., 1971). None of the subjects had coronary heart disease or peripheral vascular disease. The relevance of these observations to patients with coronary heart disease can be determined only by investigation of such patients.

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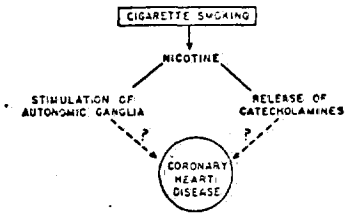
X. ACUTE AND CHRONIC EFFECTS OF NICOTINE



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The most important and widely investigated constituent of cigarette smoke is nicotine. The experimental use of this alkaloid has failed to produce coronary heart disease in animals that is similar to the human form. The pharmacologic action of nicotine can be attributed to stimulation of autonomic ganglia and the release of catcholamines. However, each mode of action taken singly has not been demonstrated to produce coronary insufficiency, experimental hypertension, atherosclerosis and thrombosis. Hyperlipidemia can be induced by catecholamines or nicotine but these same agents do not produce atherosclerosis unless the animal has also received a diet high in cholesterol.

The cardiac effects of nicotine do not in lude coronary vasoconstriction. However, it produces stimulation of the heart, which is potentially dangerous to a patient with coronary heart disease. The dose of nicotine used in the

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laboratory is so large that it is not yet possible to relate the cardiac effects to smoking by the patient with coronary heart disease.

The pharmacology of nicotine is discussed in the following Additional Bibliographic Lists:

List No. 25. Nicotine on isolated heart.
List No. 26. Release of catecholoamines from the heart.
List No. 27. Release of catecholamines from adrenal medulla.
List No. 28. Central nervous system effects of nicotine.

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X. CARDIOVASCULAR EFFECTS OF NICOTINE

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X. CARDIOVASCULAR EFFECTS OF NICOTINE

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X-A. Mode of Action on the Heart

The most important constituent of cigarette smoke that is responsible for its cardiac action is nicotine. The amount of nicotine absorbed in the respiratory tract ranges from 63 to 95%, depending on the duration of the period between inhalation and exhalation and the depth of the former (Larson, 1960). The percentage was derived by analyzing the content of nicotine in the smoke prior to and after the puff. The total amount of nicotine absorbed has also been estimated by analysis of urine for nicotine content (Beckett, 1967; Kershbaum et al., 1967; Cederlöf and Edfors, 1968). The mode of action of nicotine is as follows:

1. Nicotine effect on autonomic ganglia. Nicotine stimulates both groups of autonomic ganglia, the parasympathetic and the sympathetic. These ganglia are recorded as containing cholinergic fibers, a term introduced by Dale (1933) to indicate that acetylcholine is the chemical mediator. The result is either bradycardia from stimulation of parasympathetic ganglia, or tachycardia from stimulation of sympathetic ganglia (Aviado, 1972).

2. Release of catecholamines. The term nicotinic includes not only ganglionic stimulation (see above) but also the release of catecholamines in the adrenal medulla and in the area of adrenergic nerve endings in the heart (see Additional Bibliographic List No. 27). The release occurs not only following the administration of nicotine, but also following cigarette smoking (Westfall and Watts, 1963; Klensch, 1966; Klensch et al., 1967; Schievelbein and Werle, 1967). The end result is stimulation of the heart similar to the

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effect of epinephrine and norepinephrine (Lickint, 1959; Robin et al., 1969).

3. Neuropharmacological and biochemical effects. Nicotine, like epinephrine, increases the excitability of the heart (Frommel, 1928). There is also an increase in duration of the action potential of isolated rat atrial muscle unrelated to changes in rate and contractility (Shibata et al., 1968). In the dog ventricle a defect in conduction occurs and appearance of fibrillation following the injection of nicotine or inhalation of cigarette smoke (Webb, 1968; Greenspan et al., 1969). There are changes in myocardial metabolism and lysosomal enzymes resulting from the addition of a toxic dose of nicotine (Brachfeld and Oran, 1966; Brachfeld et al., 1967). The dose used is not normally encountered in ordinary smoking.

4. Cardiac necrosis. Large doses of nicotine administered in conjunction with isoproterenol cause necrosis of the rat heart (Wenzel et al., 1964; Wenzel and Stark, 1965, 1966; Wenzel, 1967). The interaction between isoproterenol and nicotine is attributable to the release of catecholamines by the latter. Several adrenergic blocking drugs are available and they have not been applied to the investigation of how nicotine produces cardiac necrosis (Papp and Solti, 1959; Papacostas and Reed, 1966; Shanks, 1966).

5. Chemoreceptors and chemoreflexes. The administration of large doses of nicotine brings about a stimulation of chemoreceptors in the carotid and aortic bodies (Stern et al., 1964; Hashimoto et al., 1964; Stern and Rapaport, 1967). The epicardial surface of the heart contains receptors which are activated by topical administration of nicotine (Sleight, 1964; Bergel and

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Makin, 1966, 1967). The responses to stimulation of chemoreflexes in the heart and the chemoreceptors in the carotid and aortic bodies are variable and include tachycardia or bradycardia and coronary vasoconstriction or vasodilatation. In the pulmonary circulation, the response to nicotine is the outcome of stimulation of chemoreflexes and release of catecholamines (Larson and Murray, 1963; Stern and Braun, 1966; Samaněk and Aviado, 1966). It has also been demonstrated that smoke inhalation in the dog causes the release of histamine which may in turn influence the heart (Aviado et al., 1966).

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X-B. Experimental Coronary Insufficiency

The early experiments showed that nicotine causes coronary vasoconstriction in the perfused isolated heart (Laubry et al., 1933; Wegria, 1951). In the dog coronary vasoconstriction could not be elicited by nicotine injected directly into the coronary artery of an intact heart (West et al., 1958, 1962; Bellet et al., 1960a), intravenously in the intact animal (Kien et al., 1957; Forte et al., 1960), or in the perfused canine heart (Leaders and Long, 1962), and in the heart-lung preparation (Folle et al., 1966).

Bing and his collaborators have systematically examined the effects of nicotine on the coronary circulation. Their experiments relating to the acute effects of cigarette smoking on the human heart are discussed in Section IX-B. In the animal heart, they measured capillary blood by means of radioactive iodinated albumin. Nicotine did not influence coronary capillary blood flow in the dog heart, unless the dose was large enough to influence blood pressure (Rakuson et al., 1968; Rival and Mathes, 1969). By means of radioactive Rubidium for estimating effective coronary flow, Leb et al. (1970) noted that after nicotine injection there was a significant correlation between supply of oxygen (effective blood flow) and oxygen demand of the myocardium. By direct visualization of the coronary capillaries, an increase was noted in the movement of red blood cells on the surface of the cat heart following the injection of nicotine (Bing et al., 1971; Hellberg et al., 1972; Pachinger et al., 1972). There is no evidence that nicotine causes coronary insufficiency in the normal heart.

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In some investigations performed on the dog heart with ischemia, Bellet et al. (1960b) observed that the increase in coronary blood flow in response to nicotine was considerably less in the ischemic heart as compared with the normal heart. A reduction in capillary blood flow of the ischemic heart following nicotine injection has been observed by Corsini et al. (1968) and Mathes and Rival (1971). A reduction in response to nicotine has also been observed in the atherosclerotic rabbit heart (Travell et al., 1960) and in the heart with pitressin-induced spasm (Kareva, 1963). The avian hearts show only a vasoconstrictor response to epinephrine, whereas the hearts of other species show a vasodilation (Juhasz-Nagy et al., 1965).

The increase in coronary blood flow following nicotine injection is accompanied by an increase in cardiac output in the dog (Corbascio and West, 1960; Larson et al., 1965). This effect is the outcome of positive chronotropic (Nadeau and James, 1967; Ross and Blesa, 1970) and positive inotropic action of nicotine (Puri et al., 1967, 1968). The phenomenon occurs also in man following the injection of nicotine (Boyle et al., 1947; Schweizer et al., 1960; Dock, 1963; Valori et al., 1964; Solti et al., 1964).

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X-C. Experimental Hypertension

Nicotine causes vasoconstriction of the extremities. This effect has been demonstrated in normal subjects following injection of nicotine into the brachial artery (Stromblad, 1959; Whelan,, 1968) or after it has been injected intravenously (Rottenstein et al., 1960; Solti et al., 1966). Vasoconstriction in response to nicotine has also been noted in the bat wing (Martz et al., 1970) and in the mesenteric vessels of the cat (Saphir and Rapaport, 1969) and of the rat (Balourdas, 1966; Albertini et al., 1967). There was no reduction in blood flow in rat skeletal muscle (Rakusan, 1967) and human brain vessels (Solti et al., 1963).

Several attempts have been made to develop hypertension in animals receiving nicotine for an extended period of time. Wenzel et al. (1964) treated rats for 55 weeks and observed first an elevation and then a depression of systolic pressure. Ahtee and Mattila (1966) failed to produce chronic hypertension. The only successful attempt is that of Bhagat (1968). Individuals who are habitual smokers have a lower mean blood pressure than nonsmokers (see Section IX-B). A possible explanation has been suggested by observations of Bhagat et al. (1971) that in dogs nicotine causes vasodilation by a central action and by stimulation of beta adrenergic receptors through the catecholamines released during exposure to cigarette smoke.

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